inventory will allow the United States to avoid requesting a 2008 exemption, or to significantly reduce the amount requested. Therefore, we estimate the final regulation will reduce CFC use by 1200 metric tons per year after the end of 2008, a benefit that will continue beyond the evaluation period.

In an evaluation of its program to administer the Clean Air Act, EPA has estimated that the benefits of controlling ODSs under the Montreal Protocol are the equivalent of $6 trillion in current dollars. However, EPA's report provides no information on the total tons of reduced emissions or the incremental value per ton of reduced emissions. EPA derived its benefits estimates from a baseline that included continued increases in emissions in the absence of the Montreal Protocol. We have searched for authoritative scientific research that quantifies the marginal economic benefit of incremental emission reductions under the Montreal Protocol, but have found none conducted during the last 10 years. As a result, we are unable to quantify the environmental and human health benefits of reduced ODS emissions from this regulation. Such benefits, in any event, were apparently included in EPA's earlier estimate of benefits.

As a share of total global emissions, the reduction associated with the elimination of albuterol CFC MDIs represents

only a small fraction of 1 percent. Current allocations of CFCs for albuterol MDIs account for about 0.1 percent of the total 1986 global consumption of CFCs (Ref. 5). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits because that estimate reflects future emissions growth that has not occurred.

Although the direct benefits of this regulation are small relative to the overall benefits of the Montreal Protocol, we believe the reduced exposure to UV-B radiation that will result from these reduced emissions will help protect public health. However, we are unable to assess or quantify specific reductions in future skin cancers and cataracts associated with these reduced emissions.

b. Returns on investment for environmental technology. Establishing a phaseout date prior to the expiration of patents on albuterol HFA MDIs not only rewards the developers of the HFA technology, but also serves as a signal to other potential developers of ozone-safe technologies. In particular, such a phaseout date would preserve expectations that ~~that~~ the government protects incentives to research and develop ozone-safe technologies.

Newly developed technologies to avoid ODS emissions have resulted in more environmentally "friendly" air conditioners, refrigerants, solvents, and propellants, but only after significant investments. Several manufacturers have claimed development costs that total between $250 million and $400 million to develop HFA MDIs and new propellant-free devices for the global market (Ref. 11).

These investments have resulted in several innovative products in addition to albuterol HFA MDIs. For example, breath-activated delivery systems, dose counters, dry powder inhalers, and mini-nebulizers have also been successfully marketed. This technology could also affect other drugs used for the treatment of asthma and COPD because of the likelihood that, eventually, CFCs will not be available for any drug use. To compare the effect of alternative phaseout dates on these returns to investment, we compare the ratio of the present value of increased revenues expected to accrue to innovative firms from a December 31, 2008, phaseout date and the present value of the future revenue stream of alternative phaseout dates, using both 7 percent and 3 percent annual discount rates. This ratio can provide a basis for relative assessments of the returns to investors for alternative phaseout dates. We present estimates of this ratio in a later discussion of alternatives.

Returns on investment are very sensitive to the current market prices in the United States. The pharmaceutical markets of other Parties to the Montreal Protocol operate with implicit or explicit price controls. These controls have depressed the potential returns to technological innovation. For example, in 2003, the ex-manufacturer prices (the prices of the drugs when they leave the production facilities) of the albuterol HFA MDIs most widely sold in France, Germany, and the United Kingdom ranged between roughly $3.30 and $6.40; in the United States these prices were in the neighborhood of $29 to $30.[16]

c. International cooperation. The advantages of selecting a date that maintains international cooperation are substantial because the Montreal Protocol, like most international environmental treaties, relies primarily on a system of national self-enforcement, although it also includes a mechanism to address noncompliance. In addition, compliance with its directives is subject to differences in national implementation procedures. Economically less-developed nations, which have slower phaseout schedules than developed nations, have emphasized that progress in eliminating ODSs in developing nations is affected by observed progress by developed nations, such as the United States. If we had adopted a later phaseout

[16] Analysis completed by FDA based on information provided by IMS Health, IMS MIDAS™, U.S., Germany, France and the United Kingdom, 2003.

date, other Parties could attempt to delay their own control measures.

3. Costs of the Final Rule

The effects of the final rule include increased spending for needed albuterol medication. The social costs of the final rule include the lost benefits of albuterol use that may result from the price increase. We discuss the increased spending and then the social costs in turn.

In the absence of this regulation, we would expect 430 million generic albuterol MDIs to be sold during the entire period between December 31, 2008, and December 2017, when the last patent listed in Orange Book for an albuterol HFA MDI will expire. Of these, 96 million would be sold before 2010, an earlier date when generics might arrive ~~if patents that expire in later years were deemed invalid~~. These figures are based on the estimate that approximately 96 percent (Ref. 10) of the approximately 50 million albuterol MDIs sold per year (Ref. 11) are generic, suggesting that about 48 million generic albuterol MDIs are sold annually.

With this regulation, patients who would have used generic albuterol CFC MDIs are expected generally to switch to albuterol HFA MDIs. We estimated in section V.C.6 of this document a weighted average price difference at retail pharmacies (across

all payer types) of about $26 between these products. If this difference can be applied to future transactions involving 48 million generic albuterol MDIs annually (less the 2 million free samples promised by GSK and decreased demand of 300,000 to 900,000 MDIs resulting from price increases--as calculated later in this analysis), then increased expenditures from consumers and private or public third-party payers would reach about $1.2 billion per year. This estimate is based, in part, on estimated increases in Medicaid prices that do not take into account rebates given directly to States by drug companies. To the extent that such rebates are larger for branded albuterol MDIs, which are more expensive, the increased expenditures are overestimated.

The present value of these increased expenditures in 2005 is about $6.2 billion using a 7 percent annual discount rate and $8.3 billion using a 3 percent annual discount rate. In estimating this increased spending, we focus on the period between December 31, 2008, and December 2017, when the last patent listed in Orange Book will expire. We also ignore the fact that after a VENTOLIN HFA MDI is first used, it expires much more quickly than a PROVENTIL HFA MDI or albuterol CFC MDIs. Although this change in the usable life of some MDIs may affect the quantity consumed, we are unable to quantify the magnitude of such an effect.

These increased expenditures represent primarily transfers from consumers and third-party payers, including State and Federal Governments, to branded pharmaceutical manufacturers; they are, therefore, not net costs to society. Because these estimates are based on average retail prices, they include additional spending that will go to parties other than innovative manufacturers, such as distributors and retail pharmacies. We estimate that about 11 percent of this increase--about $130 million annually--may be paid by uninsured customers ($130 million) (Ref. 10). We derive these estimates assuming increased spending is the product of the number of albuterol MDIs sold for cash and the difference between the average price for generic albuterol MDIs and the simple mean of the prices for albuterol HFA MDIs. We estimate that 5 million generic albuterol MDIs are sold to uninsured patients annually and that retail cash prices for albuterol MDIs will rise by about $27 per MDI (details of these estimates follow later in this section.) Taking in to account savings from coupons and free samples, uninsured albuterol users would therefore spend about $120 million more each year.[17]

According to MEPS, private nongroup and uninsured individuals used, on average, 3.3 albuterol prescriptions per

[17] (5 million MDIs - 300,000 free sample MDIs) x ($25/MDI) - (450,000 coupons) x ($10) = $117,500,000. Here, we assume coupons and free samples reach

year (Ref. 12). Based on IMS data, we estimate the average albuterol prescription is for 1.2 MDIs (Ref. 10). The average uninsured, or underinsured, albuterol user would therefore use about 4 MDIs/year. Based on these figures, we estimate that a population of uninsured albuterol users of about 1.25 million[18] would pay, on average, $95 more per year for albuterol.[19] This estimate does not take in to account the reduced use of albuterol MDIs among the uninsured that may result from higher prices or the extent to which quicker expiration of some HFA albuterol MDIs, relative to CFC MDIs, will increase albuterol MDI demand and expenditures. In the future, some fraction of these cash payers will likely be covered by Medicare (Ref. 10).

We expect price increases resulting from market withdrawal of less expensive generic albuterol MDIs will reduce albuterol use by several hundred thousand MDIs annually (as explained below), although there is substantial uncertainty about these estimates. The impact of this reduction on health outcomes is too uncertain to quantify given available data. Some patients, however, respond to price increases for medications for chronic conditions in ways that may adversely affect their health. A recent article found that:

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uninsured albuterol users in proportion to estimates of the uninsured fraction of the overall population (15 percent).

[18] (5 million MDIs) / 4 MDIs per uninsured user = 1.25 million uninsured users.

> copayment increases led to increased use of emergency department visits and hospital days for the sentinel conditions of diabetes, asthma, and gastric acid disorder: predicted annual emergency department visits increased by 17 percent and hospital days by 10 percent when copayments doubled * * *.

However, the article proceeds to characterize these results as "not definitive." (Ref. 4) This finding suggests that increased prices for albuterol may lead to some adverse public health effects among the populations that would face increased prices. This evidence is insufficient to permit us to quantify any adverse public health effects. We use expected reductions in albuterol MDI purchases as a surrogate measure of the impact.

Our approach to estimating the effects of the rule assumes that the primary effect of an elimination of albuterol CFC MDIs from the market would be an increase in the average price of albuterol MDIs. Given the price increase expected from the elimination of generics and existing estimates of market responses to price increases, we have projected how the quantity of albuterol MDIs consumed may decline as a result of this rule. As in the proposal, we assume that the reduction in the use of albuterol MDIs attributable to this rule can be calculated as the product of the sensitivity of use with respect to the price increase, the baseline use of albuterol MDIs among price-

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[19] ($117,500,000) / (1.25 million uninsured users) = $94.00 per uninsured

sensitive patients, and the price increase in percentage terms. We discuss these in turn.

We have no information about how consumers react to increases in the price of MDIs per se or to increases in the price of "rescue" types of MDIs, such as albuterol, in particular. Economists have researched the response of consumers to higher insurance copayments for drugs in general. The results appear to indicate price elasticities in the range of -.1 to -.2, meaning that a 10 percent increase in insurance copayments appears to lead to a reduction in the number of prescriptions of between 1 and 2 percent (Ref. 13). Some researchers have reported estimates of price elasticities as great as -.3 for asthma drugs (Ref. 4), but the authors report that there is wide variance based on the availability of over-the-counter substitutes. For example, for drugs with no over-the-counter substitute--a set that presumably includes albuterol--the reported price elasticity was -.15.[20] We have used price elasticities of between -.05 and -.15 to estimate the potential effect of price increases on demand. We recognize that elasticity estimates derived from insurance copayment

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user.

[20] Some patients may view PRIMATENE, an epinephrine MDI available over the counter, as a substitute for prescription albuterol MDIs. If this view is widespread, the decline in albuterol MDI use may be greater than that estimated here. However, insofar as PRIMATENE is effective in treating asthma, the adverse health effects would not be greater. We lack data to evaluate patients' willingness to substitute PRIMATENE for albuterol MDIs.

studies may not be specifically applicable to the effects of average retail price increases on uninsured patients' demand for albuterol.

To derive an estimate of the number of albuterol MDIs not sold as a result of this rule, we need an estimate of the baseline use of albuterol MDI sales by price-sensitive consumers. From data on retail sales by payer type from the first half of 2004, we find about 5 million generic albuterol MDIs are sold to uninsured patients annually. This estimate includes sales to people over age 65 not covered by Medicaid who we expect will be covered by Medicare in the future, but it excludes mail order and Internet sales and sales through hospitals and nursing homes. Alternatively, if uninsured individuals under age 65 use albuterol MDIs in proportion to their share of the population (roughly 15 percent) (Ref. 14), then roughly 7 million of 46 million generic albuterol MDIs would be sold to the uninsured (46 million = 48 million generic albuterol MDIs - 2 million free samples).

Finally, to estimate the price increase from this rule, we first assess IMS data, which indicate that cash payers paid, on average, $19.10 for generic albuterol MDIs and $46.30 for albuterol HFA MDIs, a difference that would suggest a price increase of $27.20 per MDI, or 142 percent. However,

alternative assumptions about the future market share of different albuterol HFA MDI manufacturers would result in a smaller price increase--130 percent. These estimated price differences faced by cash payers are only a proxy for price differences faced by uninsured patients, because some people with insurance may pay cash, and some uninsured patients may buy drugs from mail-order and Internet pharmacies.

We believe that estimates of the recent price premium for albuterol HFA MDIs may be a reasonable approximation of the price increase anticipated from this rule, at least to the extent that patent protection and the more costly criteria for FDA approval of albuterol HFA MDIs substantially curb competition. At least one listed patent is expected to expire in December 2017. While increased competition from new patented albuterol HFA MDIs may reduce future albuterol HFA MDI prices, ~~to the extent that all albuterol HFA MDI manufacturers manufacture under a single patent,~~ such reduction may be small until generic albuterol MDIs are reintroduced into the market. Apart from any patents, marketing of new albuterol HFA MDIs before the patents expire requires FDA approval of a completed NDA. After the patents expire, FDA can approve generic albuterol HFA MDIs by the abbreviated new drug application (ANDA) process. The NDA process is more complicated, expensive, and time consuming than the abbreviated new drug application

(ANDA) process by which new generic drugs are brought to market. This NDA requirement constitutes a barrier to entry in the market that will tend to further limit competition until the patents expire as compared to markets where generic drugs can be marketed. Finally, as noted earlier, one manufacturer has also announced a voluntary price freeze on its albuterol HFA MDI until 2008.

We combine different measures of price elasticities (-.05 to -.15), the size of the uninsured generic albuterol MDI market (5 to 7 million MDIs), and estimated price increases (130 percent to 140 percent) to estimate the impact of price increases on use. For example, assuming a price elasticity of - .15 and 6 million generic albuterol MDIs sold to the uninsured annually, a 130 percent price increase would reduce demand for albuterol MDIs from the uninsured by about 1.2 million MDIs annually (6 million x -.15 elasticity x 130 percent price increase = 1,200,000 MDIs). These preliminary estimates do not take into account offsetting increases in consumption from changes in promotional efforts already announced by GSK. We also note that the elasticity estimates are based on relatively small price changes and may not be applicable to large price changes such as these.

Manufacturers have announced programs to distribute free samples and coupons to mitigate any adverse effect of higher prices on utilization. For example, GSK has committed to provide 2 million albuterol HFA MDIs each year to physician offices in expectation that they would be distributed to patients in need (03P-0029/CR1, p. 7). In addition, GSK has committed to annually providing 3 million coupons worth $10 each in rebates for VENTOLIN HFA to any patient. Both GSK and Schering currently operate outreach programs that assist patients to obtain needed medications, but we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future.

Free samples and coupons help mitigate adverse impacts on uninsured patients only to the extent that they are distributed to physicians and other health care professionals who then give them to uninsured individuals.[21] To assess how free samples and coupons might affect albuterol MDI use, we conducted a thorough review of the relevant peer-reviewed literature and found two pertinent articles. One found that, while 54 percent of the free samples were actually distributed to patients, only 9 percent of the patients who received free samples were uninsured (Ref. 15). These data suggest that 4.8 percent of the free

samples were actually distributed to uninsured patients. Assuming this estimate is applicable to the albuterol HFA MDIs distributed by the GSK program, then about 96,000 albuterol HFA MDIs per year would reach the uninsured. The second article estimated that 71 percent of free samples were given to patients (Ref. 16). As an upper bound, assuming all samples are distributed to patients and that the uninsured receive them in proportion to their share of the population, approximately 300,000 MDIs (15 percent of 2 million) would reach the uninsured each year.

We expect coupons will do relatively little to improve access to albuterol among the uninsured. If 150,000 (5 percent (Ref. 15)) to 450,000 (15 percent) of the 3 million coupons reach uninsured patients each year and 100 percent of them are redeemed, this would increase albuterol MDI consumption by roughly 2,000-15,000 MDIs per year, based on the range of price elasticities considered.

Taking into account the offsetting effect of free samples and coupons, we focus on a range of 300,000 to 900,000 fewer albuterol MDIs sold each year as a result of increased prices stemming from removal of generic albuterol MDIs from the market. This assessment does not take into account Schering's and GSK's

[21] We found no information addressing how pharmaceutical companies distribute free samples among physicians and clinics, but assume that GSK will not

patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. Over the course of the evaluation period, this would equal between 2.7 million and 8.1 million fewer albuterol MDIs sold. We recognize that due to varying measures of the size of the generic albuterol MDI market for the uninsured, uncertainty about the magnitude of price increases, consumers' response, and the impact of free samples and coupons, and other factors, the true impact of the rule could fall outside this range.

4. Effects on Medicare and Medicaid

In order to apportion the possible spending increases described above to the Medicaid and Medicare programs, FDA and the Centers for Medicare & Medicaid Services (CMS) have analyzed utilization data related to Medicaid and Medicare, as well as Medicaid program spending data. As explained below, these data suggest that, were this rule in effect in 2003, Medicaid spending (including spending by States) would have increased by approximately $100 million for that year. In addition (based on 2001 utilization and 2004 prices), it would have increased drug spending on Medicare beneficiaries by roughly $240 million,

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systematically channel free samples away from low-income areas.

although this estimate includes copayments and coinsurance paid by individuals and may be too low because the estimate does not take into account increases in utilization associated with the increase in insurance coverage. These data yield the very rough estimate that the rule would increase Medicare and Medicaid spending by $340 million annually relative to a situation where access to generic albuterol CFC MDIs continued.

a. Medicaid. Medicaid spending on albuterol MDIs would have been higher by roughly $100 million in 2003--after taking into account rebates from drug companies--if albuterol CFC MDIs were not available. CMS estimates that 58 percent of this amount would be paid by the Federal Government and 42 percent by States.

Deriving this cost estimate required making some adjustments to available data. Our point of departure is the State Drug Utilization Data, available at http://www.cms.hhs.gov/medicaid/drugs/drug5.asp for 2003. These data on utilization and spending on drugs paid for by the Medicaid program suggest that State reimbursements under Medicaid would have been approximately $127 million higher in 2003 if no albuterol CFC MDIs were available (that is, if only albuterol HFA MDIs were available). This estimate assumes substitutes for all albuterol CFC MDIs were purchased at the weighted average price of albuterol HFA MDIs. However, it does

not take into account the effect of the rebates from drug companies to States and the Federal Government. CMS estimates that Medicaid program rebates constitute roughly 20 percent of gross spending on prescription drugs under the Medicaid program, suggesting that Medicaid spending on albuterol MDIs after rebates would have been roughly $100 million higher in 2003 if albuterol CFC MDIs were not available. It is important to note that this is a rough estimate, as rebates for a specific drug may differ from the 20 percent estimate. Incomplete data for 2004 suggest that comparable estimates for 2004 are higher but we believe that these are not reliable because of the incompleteness of the data.

b. Medicare. Our analysis of the impacts of this rule on Medicare addresses: (1) The total utilization of albuterol MDIs, (2) the likely price increase, and (3) the aggregate spending increase.

CMS estimates that noninstitutionalized Medicare beneficiaries not eligible for Medicaid drug coverage filled about 8 million prescriptions for albuterol MDIs (including VENTOLIN and PROVENTIL) in 2001, based on the Medicare Current Beneficiary Survey (MCBS) and with an adjustment for under-reporting for aggregate analysis purposes. As noted below, this estimate is based on Medicare beneficiaries' self-reported outpatient prescription drug utilization, including

prescriptions filled at both retail and mail order pharmacies. In addition, the adjustment for underreporting is normally used for aggregate use or spending data in MCBS and may not necessarily reflect actual underreporting for albuterol.

This analysis used data from the 2001 MCBS, a continuous, multipurpose survey of a nationally representative sample of Medicare beneficiaries. The survey is focused on health care use, cost, and sources of payment. No "paid claims" data on use of albuterol MDIs exist because Medicare will pay for albuterol MDIs only after the implementation of the new Medicare outpatient prescription drug benefit in January 2006. MCBS is the largest nationally representative set of data available on prescription drug utilization and spending by Medicare beneficiaries. The MCBS data have been used by both CMS's Office of the Actuary and the Congressional Budget Office to prepare estimates related to the new Medicare prescription drug benefit. However, because the data are self-reported, there are considerable limitations, most notably underreporting. CMS has studied the underreporting in the survey and has developed methods to adjust the data. For purposes of the estimates done for the Medicare drug benefit, the data on drug spending are analyzed in the aggregate (that is, for large collections of drugs). Estimates of individual drug product utilization and

spending, however, may be even more vulnerable to the limitations inherent in self-reported utilization data.

A reliable assessment of impacts must avoid double counting of people who are eligible for both Medicaid and Medicare. With the implementation of the new Medicare prescription drug benefit, payment for outpatient prescription drugs on behalf of Medicare beneficiaries who are also eligible for prescription drug benefits under Medicaid will be moved from the Medicaid program to the Medicare program. For purposes of this analysis, this population of dually eligible beneficiaries (that is, Medicare beneficiaries also eligible for full-benefits under Medicaid) is excluded from the analysis of the MCBS data, since their albuterol MDI utilization is captured within the Medicaid data. Approximately half of total Medicaid prescription drug spending is for this dually eligible population. However, the proportion will vary based on the type of drug involved. It is worth noting that albuterol MDIs are used to treat asthma in both the aged and disabled in the Medicare/Medicaid dually eligible population, as well as to treat asthma in children, who make up a large share of Medicaid beneficiaries.

For purposes of this analysis, we assess only data for the time periods for which data are available and we do not make projections for future years. As was noted in the impact analysis for the proposed rule on the Medicare prescription drug

benefit (69 FR 46731, August 3, 2004), there is considerable uncertainty in making estimates when there is no program experience from prior years. This uncertainty is exacerbated in the context of making estimates related to a particular drug. For example, in the context of preparing aggregate estimates for the Medicare drug benefit, CMS makes assumptions about how increased coverage induces greater utilization and, based on the National Health Expenditures, projects growth in per capita drug spending. But making such calculations for a specific individual drug would be difficult and not likely reliable. Furthermore, in the case of albuterol MDIs, the drug is subject to large annual fluctuations in demand per user and size of population using the drug due to the nature of the conditions being treated, such as asthma where acute episodes may vary by environmental factors (for example, allergies), prevalence of infectious diseases (for example, colds), and seasonal weather conditions (for example, temperature-related bronchial conditions). In addition, analyzing the effect on Medicare of a change related to one drug is further complicated, for example, by the need to consider the interactions with beneficiary cost-sharing in the context of the Medicare drug benefit design and the availability of additional low-income subsidies for certain populations. Also, the introduction of an albuterol HFA MDI from IVAX is expected to increase competition in the market to

some extent, potentially dampening anticipated price increases in part. Our estimates, therefore, apply only to past years.

We believe that prices paid by private insurers offer a potentially reasonable approximation of prices negotiated in the context of a privately administered risk-based insurance program such as the new Medicare Part D drug plans. Using proprietary data from IMS Health, we determined that prices for patients with third-party insurance were on average about$30 more per prescription for albuterol HFA MDIs than for albuterol CFC MDIs, according to IMS's National Prescription Audit for the first half of 2004 (Ref. 10). This price estimate reflects transactions in U.S. retail pharmacies, excluding Internet and mail order sales. It also reflects both payments by insurers and copayments or coinsurance payments by patients. We calculate the average price per prescription for the albuterol HFA MDIs and the albuterol CFC MDIs, respectively, as the weighted average of the price per prescription of different firms' products, where the weights are the firms' shares of the total albuterol MDIs sold. Price differences per prescription are larger than price differences per MDI, because some prescriptions are for more than one MDI.

Given this estimate of the price difference that would have existed without CFC albuterol MDIs, spending by, and on behalf of, Medicare beneficiaries without Medicaid drug coverage could

have been roughly $240 million more in order to fill the 8 million prescriptions estimated to have been filled in 2001 (based on the MCBS data). This estimate is quite approximate because it relies on an estimate of albuterol MDI prescriptions from 2001 and estimates of prescription price differences from the first half of 2004. In addition, albuterol MDI use may grow as the Medicare drug benefit reduces the cost to individuals of using albuterol MDIs.

E. Alternative Phaseout Dates

In developing this rule, we considered removing the essential-use designation for ODSs in albuterol MDIs for different dates between 12 months after issuance of a final rule and December 31, 2009. As shown previously, earlier removal would increase consumer expenditures while increasing environmental benefits. A later date would reduce the potential health effect from reduced access, but also reduce the environmental benefit and potentially put at risk international cooperation. We also considered and rejected small business exemptions as inconsistent with international commitments.

Table 4 shows the effects of selecting December 31, 2005, as the effective date, and Table 5 shows the effects if we had selected December 31, 2009 (assuming continued availability of CFCs).

Table 4.--Effects of Phaseout as of December 31, 2005

Number of Affected of Albuterol MDIs (million)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate of	7-percent discount rate of
576	$11.6	$9.3	3.6 to 9.8	14,400	1.4	1.5

Table 5.--Effects of Phaseout as of December 31, 2009

Number of Affected Albuterol MDIs (million)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in Albuterol MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
384	$7.3	$5.3	2.4 to 7.2	8,400	.88	.85

F. Sensitivity Analyses

We have conducted a sensitivity analysis to address how key sources of uncertainty may affect our estimates. Our key focus is the effect of alternative dates when generic competition for albuterol HFA MDIs may begin. ~~As a result, we present the effects of a December 31, 2008, phaseout date in Table 6, assuming that generic albuterol HFA MDIs arrive in 2010.~~ In Table 6, we present estimates assuming that generic competition arrives in 2015.

Table 6.--Effects of Phaseout on December 31, 2008--Assuming Generic Entry in 2015

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout with genetic entry in 2017 = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
336	$6.7	$5.2	2.1 to 5.6	8,400	.81	.84

This analysis suggests that the eventual date that generic competition arrives will have a substantial effect on the total reduction in albuterol MDI use and the aggregate reductions in CFC emissions. Further analysis of the arrival of generic competition would require an evaluation of the legal merits of the different patents, but such an evaluation is beyond the expertise of FDA.

G. Small Business Impact

Current HHS guidance (Ref. 17) suggests that a 3 to 5 percent impact on total costs or revenues of small entities could constitute a significant regulatory impact. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, this analysis, together with other relevant sections of this document, serves as FDA's Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

1. Affected Sector and Nature of Impacts

The affected industry sector includes manufacturers of pharmaceutical products (NAICS 32514). We obtained data on this industry from the 1997 Economic Census and estimated revenues per establishment. Although other economic measures, such as profitability, may provide preferable alternatives to revenues as a basis for estimating the significance of regulatory

impacts, we do not believe it would change the results of this analysis.

The impact of this rule on generic manufacturers is the lost revenues currently generated by sales of generic albuterol CFC MDIs. While "lost revenues" are an imperfect measure, because production resources could be shifted to alternative markets, they provide a measure that suggests the magnitude of the impact.

The Small Business Administration (SBA) has defined as small any entity in this industry with fewer than 750 employees. According to Census data, 84 percent of the industry is considered small. The average annual revenue for a small entity is $26.6 million per entity. However, the agency does not have revenue information specific to the affected entities. According to retail sales in the first half of 2004, of the 22.7 million generic or relabeled annual prescriptions for albuterol, approximately 63 percent (14.3 million MDIs) were distributed by Schering, a large firm, under the Warrick label. Six different companies marketed the other 8.4 million albuterol MDIs, with three companies accounting for over 99 percent of these 8.4 million (Ref. 10). According to data collected by the Congressional Budget Office (Ref. 18), the value of shipments from manufacturers of generic drug products accounts for

approximately 35 percent of the retail price of the product. If so, revenue from 1.7 million albuterol MDIs would approximate $8.0 million per year (1.7 million prescriptions X $13.50 per generic prescription X 35 percent). Because we lack company-specific revenue data, we are unable to estimate the impact of this rule on these small entities. To the extent that generic albuterol HFA MDIs might become available prior to the removal of the essential-use designation, any impact on small entities would be mitigated.

2. Outreach

The Montreal Protocol and Clean Air Act have been in place for more than a decade. Manufacturers of albuterol CFC MDIs have long known that CFCs would eventually lose their essential-use designations for this purpose. During the proposal stage of this rule-making, we specifically solicited comments on the impact on small entities. No comments were received that explicitly addressed this issue.

H. Conclusion

This final rule could result in increased health care expenditures of ~~more than~~ about $1.2~~1~~ billion for each year between the removal of the essential-use designation and reintroduction of generic competition at patent expiration. Taking into account GSK's commitment to provide free samples and

coupons, we estimate that higher prices due to the elimination of generic competition will reduce the number of MDIs sold by between 300,000 and 900,000 per year. This estimate does not take into account Schering's and GSK's patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. In addition, each year without using CFCs in albuterol MDIs will reduce atmospheric emissions of ODSs by 1,200 metric tons and provide increased investment returns for environmentally friendly technology that may induce further gains. Removal of the essential-use designation is consistent with FDA's role in determining the essentiality of MDIs under section 601 of the Clean Air Act, and also meets U.S. obligations under international agreements. Finally, we lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities.

VI. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. U.S. Food and Drug Administration, "Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products," March 2003.

2. Penick, Brock T. et al., "Accuracy of Float Testing for Metered-Dose Inhaler Canisters," Journal of the American Pharmaceutical Association, 42:582, July/August 2002.

3. Craig-McFeely, P.M. et al., "Prospective Observational Cohort Safety Study to Monitor the Introduction of a Non-CFC Formulation of Salbutamol with HFA 134a in England," International Journal of Clinical Pharmacology and Therapeutics, 41:67-76, 2003.

4. Goldman, J. et al., "Pharmacy Benefits and the Use of Drugs by the Chronically Ill," The Journal of the America Medical Association, May 19, 2004; 291:2344-2350, 2349.

5. United Nations Environmental Programme, "Production and Consumption of

Ozone-Depleting Substances 1986-2000," 2003.

6. The Benefits and Costs of the Clean Air Act: 1990-2010, (http://www.epa.gov/air/sect812/copy.html)

7. Mannino, D.M. et al., "Chronic Obstructive Pulmonary Disease Surveillance--United States, 1971-2000," Morbidity and Mortality Weekly Report, 51(SS06):1-16, August 2, 2002.

8. American Lung Association, "Trends in Asthma Morbidity and Mortality," Epidemiology & Statistics Unit, Research and Scientific Affairs, Table 7, April 2004.

9. Mannino, D.M. et al., "Surveillance for Asthma--United States, 1980-1999," Morbidity and Mortality Weekly Report, 51(SS01):1-13, March 29, 2002.

10. Analysis completed by FDA based on information provided by IMS Health, IMS National Prescription Audit™, 2004; IMS Health, IMS MIDAS™, Q1/2004--Q2/2004. These data can be purchased from IMS Health. Please send all inquiries to: IMS Health, Attn:

Brian Palumbo, Account Manage, 660 W. Germantown Pike, Plymouth Meeting, PA 19462.

11. Rozek, R.P., and E.R. Bishko, "Economics Issues Raised in the FDA's Proposed Rule on Removing the Essential-Use Designation for Albuterol MDIs," National Economic Research Associates, August 13, 2004 (FDA Docket No. 2003P-0029/C25).

12. Agency for Healthcare Research and Quality, "Albuterol Inhalers: Prescriptions per User, Price per Prescription and Expenditure Given Use," spreadsheet prepared at FDA's request for this rulemaking, 2004.

13. Ringel, J.S. et al., "The Elasticity of Demand for Health Care," National Defense Research Institute, Rand Health, 2002.

14. U.S. Census Bureau, "Income, Poverty, and Health Insurance Coverage in the United States: 2003," Current Population Reports, U.S. Department of Commerce, August 2004, pp. 14-15.

15. Morelli, D., and M.R. Koenigsberg, "Sample Medication Dispensing in a Residency Practice," Journal of Family Practice, 34(1):42-48, 1992.

16. Peterson, M.C. et al., "Disposition of Pharmaceutical Samples from a Private Medical Clinic," Journal of the American Pharmacists Association, 44(3):397-398, 2004.

17. U.S. Department of Health & Human Services, "Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services," May 2003.

18. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.

VII. The Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by OMB under Paperwork Reduction Act of 1995 is not required.

VIII. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. While this rule may result in States increasing spending for albuterol MDIs in programs such as Medicaid, the increased spending is not a substantial direct compliance cost, as the term is used in Executive Order 13132. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Devices, Drugs, Foods.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Clean Air Act and under authority delegated to the Commissioner of Food and Drugs, after consultation with the Administrator of the Environmental Protection Agency, 21 CFR part 2 is amended as follows:

PART 2--GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 21 CFR part 2 continues to read as follows:

Authority: 15 U.S.C. 402, 409; 21 U.S.C. 321, 331, 335, 342, 343, 346a, 348, 351, 352, 355, 360b, 361, 362, 371, 372, 374; 42 U.S.C. 7671 et seq.

§2.125 [Amended]

2. Section 2.125 Use of ozone-depleting substances in foods, drugs, devices, or cosmetics is amended by removing and reserving paragraph (e)(2)(i).

OMB revisions 3/21/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. 2003P-0029]

Use of Ozone-Depleting Substances; Removal of Essential-Use Designations

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulation on the use of ozone-depleting substances (ODSs) in self-pressurized containers to remove the essential-use designations for albuterol used in oral pressurized metered-dose inhalers (MDIs). Under the Clean Air Act, FDA, in consultation with the Environmental Protection Agency (EPA), is required to determine whether an FDA-regulated product that releases an ODS is an essential use of the ODS. Two albuterol MDIs that do not use an ODS have been marketed for more than 3 years. FDA has determined that the two non-ODS MDIs will be satisfactory alternatives to albuterol MDIs containing ODSs and is removing the essential-use designation for albuterol MDIs as of December 31, 2008. Albuterol MDIs containing an ODS cannot be marketed after this date.

DATES: This rule is effective December 31, 2008.

ADDRESSES: Received comments, a transcript of, and material submitted for, the Pulmonary-Allergy Advisory Committee meeting held on June 10, 2004, the environmental assessment, and the finding of no significant impact may be seen in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:

Wayne H. Mitchell,

Center for Drug Evaluation and Research (HFD-7),

Food and Drug Administration,

5600 Fishers Lane,

Rockville, MD 20857,

301-594-2041.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction and Highlights of the Rule

We published a proposed rule in the Federal Register of June 16, 2004 (69 FR 33602) (the 2004 proposed rule), proposing to remove the essential-use designation for albuterol MDIs. Albuterol MDIs containing chlorofluorocarbons (CFCs) or other ODSs cannot be marketed without an essential-use designation. We have determined that the four criteria for removing an essential use have been met or will be met by the effective date of the proposed rule:

- More than one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;
- Supplies and production capacity for the non-ODS products will exist at levels sufficient to meet patient need;
- Adequate U.S. postmarketing use data is available for the non-ODS products; and
- Patients who medically required the ODS product will be adequately served by the non-ODS products containing that active moiety and other available products.

We have also determined that the appropriate effective date for the removal of the essential-use designation for albuterol MDIs is December 31, 2008.

We will discuss our determinations on the criteria and the effective date in section V of this document "Comments on the 2004 Proposed Rule."

II. Background

A. Albuterol

Albuterol is a relatively selective beta$_2$-adrenergic agonist used in the treatment of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD). Albuterol has the molecular formula $C_{13}H_{21}NO_3$. Albuterol is the name established for the drug by the U.S. Pharmacopeia and the U.S. Adopted Names Council. FDA uses the name albuterol, and it is the name commonly used in the United States. In most of the rest of the world, the drug is called salbutamol, which is the ~~i~~International ~~n~~Nonproprietary ~~n~~Name for the drug (the name recommended by the World Health Organization). Albuterol is widely used in its sulfate salt form, which has the molecular formula $(C_{13}H_{21}NO_3)_2H_2SO_4$. We will use "albuterol" to refer to both albuterol base and albuterol sulfate, unless otherwise indicated.

Albuterol is available in many dosage forms for the treatment of asthma and COPD. Syrups and tablets may be taken by mouth to be absorbed into the blood through the digestive tract. Albuterol drug products are marketed in various forms for inhalational use. Albuterol is available in inhalation

solutions for use in nebulizers, and was previously marketed in the United States in a compact dry-powder inhaler. Most important for purposes of this document, albuterol is marketed in MDIs, which are small, pressurized aerosol devices that deliver a measured dose of an aerosolized drug into a patient's mouth for inhalation into the lungs.

Albuterol MDIs were first approved for use in the United States in 1981, when the new drug applications (NDAs) for VENTOLIN (NDA 18-473) and PROVENTIL (NDA 17-559) albuterol MDIs were approved by FDA. The first generic albuterol MDI was approved in 1995. Albuterol MDIs have historically used the CFCs trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) as propellants.

Albuterol MDIs are among the most widely used drug products for the treatment of asthma and COPD. Because of albuterol's relatively rapid onset of action, albuterol MDIs are frequently used as "rescue" inhalers for treatment of bronchospasm during acute episodes. Albuterol MDIs can be considered lifesaving for some patients at certain times; they are very important for controlling symptoms in many more patients who suffer from asthma or COPD. We recognize and take very seriously our obligation to examine with particular care any action that ~~may~~ could affect the availability of these important drugs.

B. CFCs

CFCs are organic compounds that contain carbon, chlorine, and fluorine atoms. CFCs were first used commercially in the early 1930s as a replacement for hazardous materials then used in refrigeration, such as sulfur dioxide and ammonia. Subsequently, CFCs were found to have a large number of uses, including as solvents and as propellants in self-pressurized aerosol products, such as MDIs.

CFCs are very stable in the troposphere, the lowest part of the atmosphere. They move to the stratosphere, a region that begins about 10 to 16 kilometers (km) (6 to 10 miles) above Earth's surface and extends up to about 50 km (31 miles) altitude. Within the stratosphere, there is a zone about 15 to 40 km (10 to 25 miles) above the Earth's surface in which ozone is relatively highly concentrated. This zone in the stratosphere is generally called the ozone layer. Once in the stratosphere, CFCs are gradually broken down by strong ultraviolet light, where they release chlorine atoms that then deplete stratospheric ozone. Depletion of stratospheric ozone by CFCs and other ODSs allows more ultraviolet-B (UV-B) radiation to reach the Earth's surface, where it increases skin cancers and cataracts, and damages some marine organisms, plants, and plastics.

C. Regulation of ODSs

The link between CFCs and the depletion of stratospheric ozone was discovered in the mid-1970s. Since 1978, the U.S. Government has pursued a vigorous and consistent policy, through the enactment of laws and regulations, of limiting the production, use, and importation of ODSs, including CFCs.

1. The 1978 Rules

In the Federal Register of March 17, 1978 (43 FR 11301 at 11318), FDA and EPA published rules banning, with a few exceptions, the use of CFCs as propellants in aerosol containers. These rules were issued under authority of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321 et seq.) and the Toxic Substances Control Act (15 U.S.C. 2601 et seq.), respectively. FDA's rule (the 1978 rule) was codified as § 2.125 (21 CFR 2.125). The rules issued by FDA and EPA had been preceded by rules issued by FDA and the Consumer Product Safety Commission requiring products that contain CFC propellants to bear warning statements on their labeling (42 FR 22018, April 29, 1977; 42 FR 42780, August 24, 1977).

The 1978 rule prohibited the use of CFCs as propellants in self-pressurized containers in any food, drug, medical device, or cosmetic. As originally published, the rule listed five essential uses that were exempt from the ban. The third listed essential use was for "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation." This language describes

albuterol MDIs, so the list of essential uses did not have to be amended in 1981 when VENTOLIN and PROVENTIL albuterol MDIs were approved by FDA.

The 1978 rule provided criteria for adding new essential uses, and several uses were added to the list, the last one in 1996. The 1978 rule did not provide any mechanism for removing essential uses from the list as alternative products were developed or CFC-containing products were removed from the market. The absence of a removal procedure came to be viewed as a deficiency in the 1978 rule, and was addressed in a later rulemaking, discussed in section II.C.5 of this document.

2. The Montreal Protocol

On January 1, 1989, the United States became a party to the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, 26 I.L.M. 1541 (1987)), available at http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf.[1] The United States played a leading role in the negotiations of the Montreal Protocol, believing that internationally coordinated control of ozone-depleting substances would best protect both the U.S. and global public health and the environment from potential adverse effects of depletion of stratospheric ozone. Currently, there are 188~~6~~

[1] FDA has verified all Web site addresses cited in this document, but FDA is not responsible for any subsequent changes to the Web sites after this document has published in the Federal Register.

parties to this treaty.[2] When it joined the treaty, the United States committed to reducing production and consumption of certain CFCs to 50 percent of 1986 levels by 1998 (Article 2(4) of the Montreal Protocol). It also agreed to accept an "adjustment" procedure, whereby, following assessment of the existing control measures, the ~~part~~Parties could adjust the scope, amount, and timing of those control measures for substances already subject to the Montreal Protocol. As the evidence regarding the impact of ODSs on the ozone layer became stronger, the ~~part~~Parties used this adjustment procedure to ~~change the treaty's obligations and~~ accelerate the phaseout of ODSs. At the fourth meeting of the ~~part~~Parties to the Montreal Protocol, held at Copenhagen in November 1992, the ~~part~~Parties adjusted Article 2 of the Montreal Protocol to eliminate the production and importation of CFCs by ~~part~~Parties that are developed countries by January 1, 1996 (Decision IV/2).[3] The adjustment also indicated that it would apply "save to the

[2] The summary descriptions of the Montreal Protocol and decisions of parties to the Montreal Protocol contained in this document are presented here to help you understand the background of the action we are taking. These descriptions are not intended to be formal statements of policy regarding the Montreal Protocol. Decisions by the parties to the Montreal Protocol are cited in this document in the conventional format of "Decision IV/2," which refers to the second decision recorded in the Report of the Fourth Meeting of the parties to the Montreal Protocol on Substances That Deplete the Ozone Layer. Reports of meetings of the parties to the Montreal Protocol may be found on the United Nations Environment Programme's Web site at http://www.unep.org/ozone/mop/mop-reports.shtml.

[3] Production of CFCs in economically less-developed countries is being phased out and is scheduled to end by January 1, 2010. See Article 2a of the Montreal Protocol.

extent that the Parties decide to permit the level of production or consumption that is necessary to satisfy uses agreed by them to be essential" (Article 2A(4)). Under the treaty's rules of procedure, the ~~part~~Parties may make such an essential-use decision by a two-thirds majority vote, although, to date, all such decisions have been made by consensus.

To produce or import CFCs for an essential use under the Montreal Protocol, a ~~part~~Party must request and obtain approval for an exemption at a meeting of the Parties. One of the most important essential uses of CFCs under the Montreal Protocol is their use in MDIs for the treatment of asthma and COPD. The decision on whether the use of CFCs in MDIs is "essential" for purposes of the Montreal Protocol turns on whether: "(1) It is necessary for the health, safety, or is critical for the functioning of society (encompassing cultural and intellectual aspects) and (2) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health" (Decision IV/25). Each request and any subsequent exemption is for only 1 year's duration (Decision V/18). Since 1994 the United States and some other ~~part~~Parties to the Montreal Protocol have annually requested, and been granted, essential-use exemptions for the production or importation of CFCs for their use in MDIs for the treatment of asthma and COPD (see,

among others, Decisions VI/9 and VII/28). The exemptions have been consistent with the criteria established by the Parties, which make the grant of an exemption contingent on a finding that the use for which the exemption is being requested is essential for health, safety, or the functioning of society, and that there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of health or the environment (Decision IV/25). Phasing out the use of CFCs in MDIs for the treatment of asthma and COPD has been an issue of particular interest to the ~~part~~Parties to the Montreal Protocol. Several decisions of the ~~part~~Parties have dealt with the transition to CFC-free MDIs, including the following decisions:

- Decision VIII/10 ~~required~~ stated that the ~~part~~Parties that are developed countries ~~to~~ would take various actions to promote industry's participation in a smooth and efficient transition away from CFC-based MDIs (San Jose, Costa Rica, 1996).
- Decision IX/19 required the ~~part~~Parties that are developed countries to present an initial national or regional transition strategy by January 31, 1999 (Montreal, Canada, 1997).
- Decision XII/2 elaborated on the ~~required~~ content of national or regional transition strategies required under Decision IX/19 and indicated that any MDI for the treatment of asthma

or COPD approved for marketing after 2000 would not be an "essential use" unless it met the criteria laid out by the Parties for essential uses. (Ouagadougou, Burkina Faso, 2000).

- Decision XIV/5 requested that each ~~part~~Party report annually the quantities of CFC and non-CFC MDIs and dry-powder inhalers sold or distributed within that country and the approval and marketing status of non-CFC MDIs and dry-powder inhalers. Decision XIV/5 also noted "with concern the slow transition to CFC-free metered-dose inhalers in some Parties." (Rome, Italy, 2002).
- Decision XV/5 states that that no essential uses of CFCs will be authorized for ~~part~~Parties that are developed countries at the 17th meeting of the ~~part~~Parties (in autumn 2005), or thereafter, unless the ~~part~~Party requesting the essential-use allocation has submitted an action plan. Among other items, the action plan is required to include a specific date by which the ~~part~~Party will cease requesting essential-use allocations of CFCs for albuterol MDIs to be sold or distributed in developed countries. The action plan must be submitted before the 25th meeting of the Open-Ended Working Group[4] in the summer of 2005. (Nairobi, Kenya, 2003).

[4] The Open-Ended Working Group (OEWG) was established in 1989 at the first meeting of the parties to the Montreal Protocol held in Helsinki. The OEWG,

In addition to fulfilling our obligations under the Clean Air Act and other provisions of the Montreal Protocol, this rule is intended to provide, for purposes of Decision XV/5, the specific date after which the United States will not request essential-use allocations of CFCs for albuterol MDIs.

C. The 1990 Amendments to the Clean Air Act

In 1990, Congress amended the Clean Air Act to, among other things, better protect stratospheric ozone (Public Law 101-549, November 15, 1990) (the 1990 amendments). The 1990 amendments were drafted to complement, and be consistent with, our obligations under the Montreal Protocol (see section 614 of the Clean Air Act (42 U.S.C. 7671m)). Section 614(b) of the Clean Air Act provides that in the case of a conflict between any provision of the Clean Air Act and any provision of the Montreal Protocol, the more stringent provision will govern. Section 604 of the Clean Air Act requires the phaseout of the production of CFCs by 2000 (42 U.S.C. 7671c),[5] while section 610 of the Clean Air Act (42 U.S.C. 7671i) required EPA to issue regulations banning the sale or distribution in interstate commerce of nonessential products containing CFCs. Sections 604 and 610

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among other duties, considers proposals for amendments and adjustments to the Montreal Protocol and prepares consolidated reports based on the reports of various scientific, technical, and economic panels. These proposals and reports may subsequently be acted on by a meeting of the parties to the Montreal Protocol.

provide exceptions for "medical devices." Section 601(8) (42 U.S.C. 7671(8)) of the Clean Air Act defines "medical device" as

> any device (as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)), diagnostic product, drug (as defined in the Federal Food, Drug, and Cosmetic Act), or drug delivery system-
>
> (A) if such device, product, drug, or drug delivery system utilizes a class I or class II substance for which no safe and effective alternative has been developed, and where necessary, approved by the Commissioner [of Food and Drugs]; and
>
> (B) if such device, product, drug, or drug delivery system, has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner [of Food and Drugs] in consultation with the Administrator [of EPA]."

4. EPA's Implementing Regulations

EPA regulations implementing the Montreal Protocol and the stratospheric ozone protection provisions of the 1990 amendments are codified in part 82 of title 40 of the Code of Federal Regulations (40 CFR part 82). (See 40 CFR 82.1 for a statement of intent.) Like the 1990 amendments, EPA's implementing regulations contain two separate prohibitions, one on the production and ~~transfer~~ import of CFCs (subpart A of 40 CFR part 82) and the other on the sale or distribution of products containing CFCs (40 CFR 82.66).

The prohibition on production and ~~transfer~~ import of CFCs contains an exception for essential uses and, more specifically, for essential MDIs. The definition of essential MDI at 40 CFR

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[5] In conformance with Decision IV/2, EPA issued regulations accelerating the

82.3 requires that the MDI be intended for the treatment of asthma or COPD, be essential under the Montreal Protocol, and if the MDI is for sale in the United States, be approved by FDA and listed as essential in FDA's regulations at § 2.125.

The prohibition on the sale of products containing CFCs includes a specific prohibition on aerosol products ~~or~~ and other pressurized dispensers. The aerosol product ban contains an exception for medical devices listed in § 2.125(e). The term "medical device" is used with the same meaning it was given in the 1990 amendments and includes drugs as well as medical devices.

5. FDA's 2002 Regulation

In the 1990s, we decided that § 2.125 required revision to better reflect our obligations under the Montreal Protocol, the 1990 amendments, and EPA's regulations, and to encourage the development of ozone-friendly alternatives to medical products containing CFCs. In particular, as acceptable alternatives that did not contain CFCs or other ODSs came on the market, there was a need to provide a mechanism for removing essential uses from the list in § 2.125(e). In the Federal Register of March 6, 1997 (62 FR 10242), we published an advance notice of proposed rulemaking (1997 ANPRM) in which we outlined our then-current

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complete phaseout of CFCs, with exceptions for essential uses, to January 1, 1996 (58 FR 65018, December 10, 1993).

thinking on the content of an appropriate rule regarding ODSs in products FDA regulates. We received almost 10,000 comments on the 1997 ANPRM. In response to the comments, we revised our approach and drafted a proposed rule published in the Federal Register of September 1, 1999 (64 FR 47719) (1999 proposed rule). We received 22 comments on the 1999 proposed rule. After minor revisions in response to these comments, we published a final rule in the Federal Register of July 24, 2002 (67 FR 48370) (the 2002 final rule) (corrected in 67 FR 49396, July 30, 2002, and 67 FR 58678, September 17, 2002).

Among other changes, the 2002 final rule, in revised § 2.125(g)(3), set standards that FDA would use for determining whether the use of an ODS in a medical product is no longer essential. The 2002 final rule provided that to remove an essential-use designation, FDA must find that:

- At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;
- Supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need;

- Adequate U.S. postmarketing use data is available for the non-ODS product(s); and
- Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products.

To remove the essential-use designation of an active moiety marketed in an ODS product represented by one new drug application (NDA), there must be at least one acceptable alternative, while for an active moiety marketed in ODS products and represented by two or more NDAs, there must be at least two acceptable alternatives.

Because there are multiple NDAs for albuterol MDIs containing an ODS, the rule requires that there must be at least two acceptable alternatives available for us to remove the essential-use designation for albuterol. We have determined that there are two acceptable alternatives for albuterol MDIs containing an ODS.

FDA approved the NDA for PROVENTIL HFA, albuterol sulfate MDI, on August 15, 1996 (NDA 20-503), and the product was introduced into the U.S. market later that year. PROVENTIL HFA is manufactured by 3M Co. (3M) and marketed by Schering-Plough Corp. (Schering). VENTOLIN HFA, albuterol sulfate MDI, was approved on April 19, 2001 (NDA 20-983), and it was introduced into the U.S. market in February 2002. VENTOLIN HFA is

manufactured and marketed by GlaxoSmithKline (GSK). Both of these products use the hydrofluoroalkane HFA-134a as a replacement for ODSs. HFA-134a does not affect stratospheric ozone. We will use the phrase "albuterol HFA MDIs" to refer to both of these products in this document. IVAX Corp. (IVAX) has recently begun marketing an albuterol HFA MDI, but the short period of time that the IVAX MDI has been on the market prevents us from considering the drug an alternative to albuterol CFC MDIs for purposes of this rulemaking (see our response to comment 14). Albuterol HFA MDIs are the subject of patents, listed in our publication Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), which will, presumably, block the marketing of generic albuterol HFA MDIs until at least 2017.[6] See our response to comment 36 of this document for a discussion of the patent issues that were raised in this rulemaking.

There is a separate essential-use designation for metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use, § 2.125(e)(2)(viii). This essential use was added to the list of essential uses (§ 2.125(e)), even though albuterol and ipratropium bromide were already separately included in the list

[6] Since publication of the 2004 proposed rule, two patents that expire in 2017 have been listed in the Orange Book for VENTOLIN HFA.

of essential uses. (See 60 FR 53725, October 17, 1995, and 61 FR 15699, April 9, 1996.) The only drug product marketed under the essential-use designation for metered-dose ipratropium bromide and albuterol sulfate, in combination, is Boehringer Ingelheim Phamaceuticals' product COMBIVENT. Because COMBIVENT has two active ingredients, it is not subject to Decision XV/5, which concerns MDIs with albuterol as the sole active ingredient. This rule will not affect the essential-use status of COMBIVENT.

III. Comments on the 2004 Proposed Rule

On June 10, 2004, we held a meeting of the Pulmonary-Allergy Drug Advisory Committee (the PADAC meeting) to discuss the issues involved in removing the essential-use designation for albuterol MDIs (see the Federal Registers of May 11, 2004 (69 FR 26169), and June 2, 2004 (69 FR 31126)). Presentations were made by 13 speakers representing patient advocacy groups, medical professional organizations, an industry organization, an environmental advocacy group, an economics consulting firm, GSK, Schering, Honeywell Chemicals (Honeywell), and IVAX. We ~~will~~ address the comments made in written material submitted to the committee and oral comments made during the open public hearing and committee discussion portions of the meeting in addition to

the written and electronic comments submitted to the docket in response to the proposed rule.[7]

We ~~have~~ received over 75 written and electronic comments in response to the 2004 proposed rule. They were submitted by patients, health care providers, patient advocacy groups, professional groups, manufacturers, a law firm, an economics consulting firm, and industry organizations. Most of the parties who spoke at the PADAC meeting also submitted written comments.

A. General Comments

(Comment 1) We received several comments that expressed general approval for the 2004 proposed rule.

We appreciate the effort that the people who submitted these comments, and all other comments, made in expressing their opinions on this important rulemaking.

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[7] Fran Du Melle, Executive Vice President of the American Lung Association, submitted a citizen petition on behalf of the U.S. Stakeholders Group on MDI Transition on January 29, 2003 (Docket No. 03P-0029/CP1) (Stakeholders' petition). The Stakeholders' petition requested that we initiate rulemaking to remove the essential-use designation of albuterol MDIs. Several comments were submitted in response to the petition. All of the opinions and information in those comments, ~~W~~with one exception (see comment 39), were also contained in testimony at the PADAC meeting or in comments on the proposed rule. In nearly every case, parties submitting comments on the petition also testified at the PADAC meeting, submitted comments on the proposed rule, or both. Accordingly, with the exception of comment 39, we will not be directly responding in this document to the Stakeholders' petition or the comments on the petition. ~~However, with the exception of the comment we do discuss, we are not aware of any significant issues raised in the Stakeholders' petition or the comments on the petition that were not also raised in comments on the proposed rule or in comments made at the PADAC meeting.~~

(Comment 2) We received several comments that expressed a general opposition to the phaseout of albuterol CFC MDIs, without giving any reasons for the opposition.

We cannot address these general comments. Comments that gave specific reasons why the person submitting the comment opposes the elimination of the essential-use designation for albuterol CFC MDIs will be discussed in the appropriate sections of this document.

(Comment 3) A few comments seemed to be based on a perception that this rulemaking would remove all albuterol MDIs from the market.

The perception is inaccurate. This rulemaking is based on the fact that there will be at least two different albuterol MDIs that are acceptable alternatives under § 2.125(g) available after the rule goes into effect.

(Comment 4) Several comments were made advocating an expeditious phaseout of albuterol CFC MDIs. A few comments recommended ~~that~~ we proceed slowly and cautiously.

We believe ~~that~~ this final rule provides for the phaseout of albuterol CFC MDIs with a speed that is consistent with our duty to protect the public health and our legal obligations.

(Comment 5) One comment requested ~~that~~ we publish this rule by December 31, 2004.

~~This rule was not published~~ We did not publish this rule by December 31, 2004, —because it involves complicated and sensitive issues that required extensive consultation and deliberation within FDA and the Department of Health and Human Services (HHS), and with EPA and other Federal agencies. We have issued this rule in the most expeditious manner, consistent with the complexities and sensitivity of the issues involved.

(Comment 6) One comment asked that we consider in this rulemaking the availability of CFC drug products that do not have a non-CFC substitute, the availability of generic albuterol MDIs, and the impact that higher priced drugs may have on the public health.

As we discuss in several places in the 2004 proposed rule and this document, issues of price and generic competition were major concerns to us. However, because this rulemaking deals exclusively with the essential-use designation for albuterol MDIs, we did not examine the availability of non-CFC substitutes for drug products other than albuterol CFC MDIs.

(Comment 7) One comment stated ~~that~~ we did not adequately communicate to the medical community the details of our policy regarding CFC MDIs. The comment expressed concern that we did not give a time frame for the phaseout of albuterol CFC MDIs.

We believe ~~that~~ we have done a good job of keeping the public and the medical community informed on our policy

regarding the elimination of essential-use designations for medical products. We first discussed our general policy on the issue in the 1997 ANPRM. We received nearly 10,000 comments in response to the 1997 ANPRM, which demonstrates that this document received wide publicity. We received additional comments in response to the 1999 proposed rule, which proposed changes in 21 CFR 2.125 to provide a mechanism for eliminating essential uses. A citizen petition was submitted on behalf of the U.S. Stakeholders Group on MDI Transition (stakeholders group) on January 29, 2003 (Docket No. 03P-0029/CP1), essentially requesting that we initiate this rulemaking. This stakeholders group consists of both patient advocacy and professional organizations. These groups were aware of our policies. FDA staff has spoken several times before professional medical organizations, patient advocacy groups, and the National Asthma Education and Prevention Program Coordinating Committee of the National Institutes of Health. FDA staff have also answered countless telephone calls and correspondence on the subject. We have provided press releases and opportunities for interviews to the general, trade, and professional media. We believe we have done what can be reasonably expected to inform the public and the medical profession. However, we were not able to provide a time frame for eliminating the essential-use designation for albuterol

MDIs. We specifically solicited comments on an appropriate effective date for the elimination of the essential-use designation for albuterol MDIs. The effective date could not be established until we had finished our evaluation of the comments submitted in response to the 2004 proposed rule, prepared a draft of this document, and consulted with EPA and other Federal agencies.

B. The Same Active Moiety with the Same Route of Administration, for the Same Indication, and With Approximately the Same Level of Convenience of Use

1. The Same Active Moiety with the Same Route of Administration for the Same Indications

We did not receive any comments disagreeing with our tentative conclusions stated in the 2004 proposed rule, or addressing the conclusions in any substantive way, that albuterol HFA MDIs have the same active moiety with the same route of administration for the same indications as albuterol CFC MDIs. We therefore finalize our tentative conclusion ~~find~~ that albuterol HFA MDIs have the same active moiety with the same route of administration for the same indications as albuterol CFC MDIs.

2. Approximately the Same Level of Convenience of Use

(Comment 8) One comment asserted that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the VENTOLIN HFA MDI requires more force to operate.

Although we do have some data on the force needed to operate the various albuterol MDIs, because that information comes from different sources using different measuring techniques and apparatus, we are not able to meaningfully compare the amounts of force needed to operate albuterol HFA MDIs compared to the force needed for albuterol CFC MDIs. However, of the approximately 20 comments we received that indicated that the person submitting the comment had some experience using albuterol HFA MDIs, only one complained that the albuterol HFA MDIs required excessive effort to operate. None of the thirteen comments from health care providers indicated that their patients had problems operating the albuterol HFA MDIs. The PROVENTIL HFA MDI is somewhat shorter and wider than the VENTOLIN HFA MDI. Patients who find it difficult to apply adequate pressure to the VENTOLIN HFA MDI may wish to try the shorter PROVENTIL HFA MDI or other albuterol HFA MDIs that may come onto the market.

(Comment 9) One comment said that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the VENTOLIN HFA MDI needs to be primed before use.

The approved labeling for both PROVENTIL HFA and VENTOLIN HFA recommend that patients prime the MDI before using it for the first time and in cases where the MDI has not been used for more than 2 weeks by releasing four test sprays into the air, away from the face. The approved labeling for PROVENTIL CFC MDIs and Warwick brand albuterol CFC MDIs contain a similar instruction about priming, but recommend priming if the MDI has not been used for 4 days, as opposed to the more convenient 2 weeks for the albuterol HFA MDIs. The approved labeling for VENTOLIN CFC MDIs, and for the generic albuterol CFC MDIs which refer to the VENTOLIN CFC MDI, contain an essentially identical recommendation, but refer to the operation as "test sprays" rather than priming. These test sprays are recommended if these albuterol CFC MDIs have not been used for more than 4 weeks. Therefore, priming is recommended for all of the albuterol CFC MDI products affected by this rulemaking. The only difference between albuterol CFC MDIs and albuterol HFA MDIs that would inconvenience patients is the shorter period of non-use before priming is recommended for the albuterol HFA MDIs compared to VENTOLIN CFC MDIs and the generic albuterol CFC MDIs which refer to the VENTOLIN CFC MDI. We consider this difference be at most a minor inconvenience, and not a "significant [variation] in convenience that materially impede[s] patient compliance." See the 2002 final rule at 48377. When we compare the albuterol HFA

MDIs to PROVENTIL CFC MDIs and Warwick brand albuterol CFC MDIs, the albuterol HFA MDIs are actually more convenient, because of the longer period of non-use before priming is recommended.

(Comment 10) One comment stated that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the float test cannot be used to determine whether the VENTOLIN HFA MDI is empty.

The float test is a widely described, but inaccurate, method of ascertaining whether an MDI is empty by seeing if it floats. In addition to being an inaccurate method to ascertain whether an MDI still contains usable quantities of the drug, the float test can damage the MDI (See Ref. 1 and Ref. 2). The float test is not recommended in the approved labeling of any albuterol CFC MDI. The only accurate way to determine whether an MDI still contains usable quantities of the drug is to keep track of the number of actuations. This is true for both albuterol CFC and HFA MDIs. Therefore we cannot view the inability to perform the float test on the albuterol HFA MDIs as a "significant [variation] in convenience that materially impede patient compliance." (See the 2002 final rule at 48377.)

We find that albuterol HFA MDIs have approximately the same level of convenience of use as albuterol CFC MDIs.

C. Supplies and Production Capacity for the Non-ODS Products Will Exist at Levels Sufficient to Meet Patient Need

(Comment 11) At the PADAC meeting a representative of GSK stated ~~that~~ GSK was currently producing approximately 300,000 albuterol HFA MDIs annually at their Zebulon, North Carolina, plant. She further stated ~~that~~ the current installed capacity at Zebulon is 15 million albuterol HFA MDIs annually, but that it would take GSK 6 to 12 months after a final decision on an effective date in this rulemaking to hire staff and reconfigure existing space to take full advantage of the installed capacity. She stated ~~that~~ it would take GSK 12 to 18 months after a final decision on an effective date in this rulemaking to install additional manufacturing equipment and secure required component supplies to enable GSK to manufacture 30 to 33 million albuterol MDIs.

A representative of Schering stated at the PADAC meeting that 3M would be able to manufacture enough albuterol MDIs to meet Schering's "share of the expected demand" for approximately 50 million albuterol HFA MDIs (transcript of PADAC meeting at p. 130). Answering a question from a committee member, the Schering representative clarified that his statement regarding Schering's and 3M's share of the manufacturing capacity was consistent with the earlier statements made on behalf of GSK.

In a subsequent written comment (2003P -0029/C20), GSK revised its production estimates and stated ~~that~~ they would begin increasing production before the publication of this rule,

and that they currently anticipated having the capacity to produce 30 million albuterol HFA MDIs annually by December 31, 2005. GSK further said they will also begin building up their inventory at least 3 months before the effective date of this rule. GSK also said ~~that~~ they would reevaluate their expansion plans if the effective date of this rule were substantially beyond December 31, 2005.

Schering also revised their projections on increasing production capacity in a written comment submitted after the PADAC meeting (2003P -0029/C31). Schering said they will have adequate production available to meet demand for albuterol HFA MDIs by December 2005. Schering also said they would reevaluate their expansion plans if the effective date of this rule were substantially beyond December 2005. 3M, which produces the albuterol HFA MDIs Schering markets, ~~stated in a late comment~~ confirmed Schering's comment by stating that they will have the capacity to manufacture 30 million albuterol HFA MDIs annually by December 31, 2005.

These projections were major considerations we took into account in establishing the effective date for this rule. We discuss our rationale for setting a December 31, 2008 effective date in our response to comment 32.

(Comment 12) A comment from a manufacturer of HFA-134a stated ~~that~~ there would be more than adequate supplies of HFA-

134a for albuterol MDIs if the essential-use designation is removed.

We appreciate this confirmation that adequate supplies of HFA-134a will exist to meet the increased demand for the propellant.

(Comment 13) A few comments from patients expressed concerns that shortages of albuterol MDIs may result from the elimination of the essential-use status of albuterol MDIs. Comments from a trade organization and a chain drug store expressed concerns about whether production capacity for albuterol HFA MDIs would be in place as quickly as had been discussed in the 2004 proposed rule.

The issue of adequate supply and production capacity has been key to this rulemaking. We regard the statements by GSK, Schering, and 3M that they will have adequate production in place as the best evidence on the availability of production capacity. When we chose December 31, 2008, as the effective date of this rule, we did so with every reasonable expectation that adequate supplies and production capacity would be in place by December 31, 2008.

(Comment 14) A representative of IVAX stated at the PADAC meeting that IVAX had submitted an NDA for an albuterol HFA MDI

in January 2003, and received an approvable letter[8] from FDA for the NDA on November 28, 2003. He also said ~~that~~ IVAX had submitted a separate NDA for an albuterol HFA breath-actuated inhaler in August 2003. He said ~~that~~ he expected the products to be on the market in the near future. He stated that IVAX would soon have the capacity to manufacture 50 to 60 million HFA MDIs a year at IVAX's Waterford, Ireland, plant, although he did not specify what proportion of that capacity would be allocated to albuterol HFA products or to products for the U.S. market.

We did not consider this information in making our decision on the essential-use designation for albuterol MDIs. The IVAX albuterol HFA MDI was approved on October 29, 2004, and introduced into the market in December, 2004. Because this product has been on the market for such a short time, the available U.S. postmarketing use data is inadequate for purposes of § 2.125(g)(3)(iii). IVAX's albuterol HFA breath-actuated inhaler has not been approved or marketed. Section 2.125(g)(4)(i) requires alternative products to be marketed. In addition, because the product has not been marketed, there can be no U.S. postmarketing use data available to allow us to

[8] An "approvable letter" is a written communication to an applicant from FDA stating that we will approve the NDA if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an NDA and does not permit marketing of the drug that is the subject of the NDA (21 CFR 314.3).

evaluate whether the breath-actuated inhaler will be an acceptable alternative to albuterol CFC MDIs.

(Comment 15) One comment asserted ~~that~~ the entire supply of albuterol HFA MDIs for the United States would be produced at one GSK facility and one 3M facility. The comment concluded that adequate supplies of albuterol HFA MDIs were insufficient because it was unclear whether one facility could supply the entire market if the other facility were forced to close.

We appreciate the concerns expressed in this comment; however, the factual premise for the comment is misstated. We believe that a switch to albuterol HFA MDIs will improve the security of the U.S. supply of albuterol MDIs. Immediately after the phaseout of albuterol CFC MDIs, we will have one GSK facility and two 3M/Schering facilities supplying the U.S. market for albuterol MDIs. This compares favorably to the current situation with albuterol MDIs, where one Schering facility and one IVAX facility supply 95 percent of the U.S. market for albuterol CFC MDIs(comment from NERA dated August 13, 2004 (2003P-0029/C25)), exhibit 4; and corrected comment from GSK, dated August 25, 2004 (2003P-0029/CR1). IVAX's recently approved albuterol HFA MDI, although not considered an alternative product for purposes of this rule (see our response to comment 14), gives additional assurance that there will be adequate supplies of albuterol HFA MDIs if there is an

interruption of production at one of the GSK or 3M approved manufacturing sites. We also would like to point out that GSK and 3M have overseas production facilities that are not listed as authorized manufacturing facilities in the approved NDAs for PROVENTIL HFA and Ventolin HFA. These facilities may be able to export albuterol HFA MDIs to the United States in an emergency shortage situation.

In our rulemaking establishing the criteria for eliminating an essential-use designation, we considered requiring multiple production sites to ensure a secure supply of non-ODS drug products (see the 1997 ANPRM at 10245, the 1999 proposed rule at 47723, and the 2002 final rule at 48377). We chose not to require multiple production sites for the alternative products as a criterion for eliminating the essential-use designation. In any case, albuterol HFA MDIs can be manufactured at three or more sites, which will provide a high degree of security for continued supplies of albuterol HFA MDIs, compared to the supply of other drugs intended for treatment of serious or life-threatening diseases, many of which are only manufactured in one facility.

(Comment 16) One comment recommended ~~that~~ we delay the effective date for this rule until albuterol MDIs from IVAX and Sepracor Inc. (Sepracor) are on the market to ensure adequate supplies and provide price competition. Another comment

recommended ~~that~~ we establish an earlier effective date if the albuterol MDIs from IVAX and Sepracor Inc. are approved.

The IVAX albuterol HFA MDI is already approved (see our response to comment 14). Sepracor's levalbuterol tartrate[9] MDI XOPENEX HFA was approved on March 11, 2005, but has not been marketed by the time this document was published. However, because XOPENEX HFA has not been marketed, we cannot consider it an alternative to albuterol CFC MDIs (see our response to comment 14). While we believe that the presence of additional suppliers of non-ODS albuterol products would be desirable for the reasons given in the comment, we do not believe they are necessary for the purposes of this rulemaking. Based on statements from GSK, Schering, and 3M, we expect that adequate production capacity for alternative products evaluated under § 2.125(g) will exist by the effective date of this rule. As we discuss in our responses to comment 18 and in section V of this document, we also believe that anticipated prices for albuterol HFA MDIs will not prevent patients from being adequately served by the albuterol HFA MDIs, even without the downward price pressure of additional competition.

[9] Levalbuterol tartrate is the tartrate salt of levalbuterol, the single R-enantiomer of albuterol, which is the active ingredient in both CFC and HFA MDIs as a racemic mixture of the two stereoisomers (R and S) at a 1:1 ratio. We have not determined whether we will, in the future, consider products whose active ingredient is a stereoisomer to be alternatives to drug products whose active ingredient is the corresponding racemic mixture.

We find that supplies and production capacity for albuterol HFA MDIs will exist at levels sufficient to meet patient needs by December 31, 2008.

D. Adequate U.S. Postmarketing Use Data ~~Are~~ is Available for the Non-ODS Products

We did not receive any substantive comments about whether adequate U.S. postmarketing use data ~~are~~is available for the albuterol HFA MDIs. We therefore finalize our tentative conclusion ~~find~~ that adequate U.S. postmarketing use data ~~are~~ is available for PROVENTIL HFA and VENTOLIN HFA, the albuterol HFA MDIs that we considered as alternatives in this rulemaking.

E. Patients Are Adequately Served by the Non-ODS Products

(Comment 17) A representative of GSK speaking at the PADAC meeting described GSK's Bridges to Access program. Bridges to Access provides GSK drugs at very low cost to lower-income individuals and families. She also mentioned GSK's Orange Card Program and the Together Rx program in which GSK participates. Both of these programs allow eligible Medicare patients to purchase drugs at significantly reduced prices. She added that GSK intended to annually distribute 2 million VENTOLIN HFA MDIs to physicians as samples. She also said ~~that~~ GSK expected that many physicians would primarily provide these samples to their lower-income patients.

A subsequent written comment from GSK provided additional information on the Bridges to Access, Orange Card, and Together Rx programs. The comment also describes a Ventolin HFA Savings Check program which will distribute at least 3 million $10 coupons for use in purchasing VENTOLIN HFA MDIs.

A representative of Schering speaking at the PADAC meeting said ~~that~~ Schering's SP Cares program, which is similar to GSK's Bridges to Access program, distributes free drugs, including PROVENTIL HFA, to low-income uninsured patients.

A written comment asserted that the Bridges to Access program provided albuterol HFA MDIs to only approximately 1.4% of the uninsured patients who need albuterol MDIs, and that the program would have to be expanded to an extreme degree to provide meaningful supplies of albuterol MDIs to all uninsured patients. This comment also asserted that GSK's commitment to annually provide 2 million free albuterol HFA MDIs would have a limited benefit to the uninsured population because large numbers of uninsured patients receive medical care in the emergency departments of hospitals rather than in a physician's office, and it is unlikely that the free albuterol HFA MDIs will be distributed to the emergency departments. This comment was submitted before GSK's comment describing the Ventolin HFA Savings Check program.

Another comment stated that any patient assistance program must be targeted to those most in need, particularly low-income children and minority populations, while yet another comment stressed the importance of patient assistance programs in the transition to albuterol HFA MDIs.

We took these comments into consideration in determining that ~~all~~ patients would be adequately served by albuterol HFA MDIs. These patient assistance programs have the potential to alleviate difficulties that lower income patients may have in obtaining the higher-priced albuterol HFA MDIs.

We agree with the comment that stated that these programs must carefully target the populations most in need of financial assistance in procuring needed albuterol MDIs, and we strongly recommend that GSK and Schering take all reasonable steps to ensure that their programs serve patients with the greatest needs, regardless of whether those patients are treated in a physician's office, clinic, or hospital emergency department. This targeting is particularly important in distributing free albuterol HFA MDIs.

We believe that many of the concerns expressed by the comment critical of GSK's Bridges to Access are valid, but that the comment underestimates the positive effect that Bridges to Access and other patient assistance programs can have. The estimate in the comment did not factor in the 2 million free

albuterol HFA MDIs GSK has committed to distribute to physicians as samples and whatever free albuterol HFA MDIs Schering may distribute. The comment also could not factor in the effect of GSK's Ventolin HFA Savings Check program. With successful targeting, these free albuterol HFA MDIs and $10 coupons ~~will~~ should have a beneficial impact; with less successful targeting the impact could be very limited (see section VII.D.2 of this document). The comment also ignores the potential impact of Schering's SP Cares program, which is similar to GSK's Bridges to Access program. We recognize that the Bridges to Access and SP Cares programs will have to expand to reach all uninsured low and moderate income patients who will need albuterol HFA MDIs, but the degree of expansion required would be smaller than that described in the comment critical of the Bridges to Access program. We also believe that GSK and Schering understand the need to expand these programs, and that this understanding was implicit in their testimony at the PADAC meeting and written comments (see pp. 5-6 of GSK's corrected comment of August 25, 2004 (2003P-0029/CR1) and p. 4 of Schering's comment of August 13, 2004 (2003P-0029/C31)).

(Comment 18) A speaker at the PADAC meeting said ~~that~~ because albuterol HFA inhalers retail for $20 more than generic albuterol CFC MDIs, an early phaseout of albuterol HFA MDIs could result in a total $5 billion in additional treatment costs

until HFA inhalers come off patent. The speaker also said ~~that~~ the economic burden would fall most heavily on those Americans least able to pay the price, with a disproportionate effect on minorities, inner-city children, elderly patients on fixed incomes, and the rural poor. The speaker asserted that eliminating the essential-use designation before lower-priced generic albuterol HFA MDIs are on the market would force many lower-income patients to discontinue use of albuterol MDIs. The speaker also referred to a recent study in JAMA: The Journal of the American Medical Association indicating that increasing copayments can reduce prescription drug use up to 32 percent. She further stated ~~that~~ this would result in a cascading increase in total health care costs, as patients who discontinue their albuterol are admitted to emergency rooms and hospital wards.

A speaker representing an economics consulting firm under contract to GSK stated at the PADAC meeting that ~~all~~ patients would be adequately served by albuterol HFA MDIs. He projected ~~that~~ the average price per MDI would increase by $9.87 and ~~that~~ the yearly average cost per patient would rise by $16.02. He also said ~~that~~ adequate programs were in place to minimize the adverse impact on lower-income patients.

Several comments from patients, health care professionals, and other parties stated ~~that~~ the elimination of lower-priced

generic albuterol MDIs that would result from this rule would force many patients to discontinue the use of albuterol MDIs, with significant adverse impact on their health, increased hospitalizations, loss of time at work, and a worsening quality of life. Many of these comments recommended ~~that~~ the essential-use status of albuterol MDIs not be removed until after generic albuterol HFA MDIs are approved and marketed.

Other comments agreed with our tentative conclusion stated in the 2004 proposed rule that ~~all~~ patients will be adequately served by albuterol HFA MDIs.

While we do not agree with the statement from the speaker from the contract economic consulting firm that ~~that~~ the average price per MDI would only increase by $9.87 and that the yearly average cost per patient would only rise by $16.02, we do agree with the conclusion of the speaker that the price of albuterol HFA MDIs will not prevent patients from being adequately served. As discussed in more detail in section V, we estimate that the retail cash price per MDI would increase by $27 and the average yearly cost to uninsured patients would rise $95. While higher drug prices are undesirable, we do not believe that asthma and COPD patients will be forced to stop using albuterol MDIs because of price increases. We believe that the programs discussed in comment 17 can, if properly utilized, provide a safety net for lower-income patients who otherwise could not

afford this very important drug. Section V of this document contains a fuller discussion of the economic issues presented by this rulemaking. While we recognize that sales of albuterol MDIs may decline by approximately 1 or 2 percent as a result of this rulemaking, this decline in sales does not necessarily equate to patients having to forgo appropriate treatment of their asthma or COPD because of price increases. ~~This small decline in sales may also be attributed to the cumulative effect of several other factors,~~ There are many ways patients may modify their behavior in order to minimize the impact of elimination of generic albuterol MDIs, including: ~~patients~~ increasing their use of other asthma and COPD drugs, including non-albuterol bronchodilators (and thereby decreasing their need for albuterol); ~~patients~~ buying fewer MDIs to keep in different locations because they have chosen to limit the number of MDIs they have beyond the one patients generally carry on their person.~~;~~ ~~p~~Patients with infrequent bouts of bronchospasm may also choose~~ing~~ not to purchase albuterol HFA MDIs that the patients believe they might not use, even though the patients are financially able to do so.~~;~~ ~~and patients not availing themselves of programs discussed in our response to comment 17. While we believe that each of these events would be infrequent, cumulatively they could account for a decline in sales of 1 or 2 percent.~~

(Comment 19) A speaker at the PADAC meeting said ~~that~~ an FDA policy that removed lower priced generic drugs from the market was contrary to the intent of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman amendments). A written comment asserted ~~that~~ the real intent of this rulemaking was to remove generic albuterol MDIs from the market.

We recognize that one of consequences, although not one ~~that~~ we desire, of this rulemaking will be the removal, for a period of time, of generic albuterol MDIs from the market. We agree with the speaker at the PADAC meeting that one of the general intentions of the Hatch-Waxman amendments is to encourage the entry of lower-priced generic drug products into the market. However, another key purpose of the Hatch-Waxman amendments is to encourage significant innovations in human drugs (see generally 130 Cong. Rec. H9113-14 and H9121-22 (Sept. 6, 1984) (statements of Rep. Waxman)). The development of HFA inhalers represents large investments of time and money by innovator firms. This investment resulted in innovative products that significantly serve the public health by protecting the stratospheric ozone. While the provisions of the Hatch-Waxman amendments do not directly apply to this rulemaking, the underlying general policy of encouraging innovation and protecting investment in research and development

does apply as much as the policy of encouraging the availability of lower-priced generic drugs. Most importantly, there is no specific provision in the Hatch-Waxman amendments that prohibits us from removing generic albuterol MDIs from the market. There is, however, specific language in the Clean Air Act (42 U.S.C. 7671) that requires us to evaluate whether a use of an ozone-depleting substance in a drug product is, or remains, an essential use. We are obligated to follow the specific mandate Congress gave us in the Clean Air Act, rather than one of two general policies underlying another piece of legislation.

(Comment 20) One comment suggested ~~that~~ we approve generic albuterol HFA MDIs immediately, to lower expenses incurred by asthma patients.

Albuterol HFA MDIs are the subject of patents that may affect the availability of generic albuterol HFA MDIs —until they expire~~at least 2017~~. FDA's ability to approve generics is constrained by the patent and exclusivity protections afforded by the Hatch-Waxman amendments. FDA may not approve generic albuterol HFA MDIs before permitted by law.

(Comment 21) One comment expressed concern that the removal of the essential-use designation for albuterol MDIs would lead to higher costs to the Federal Government as a result of the Medicare prescription drug benefits that will go into effect on January 1, 2006 (see Title I of the Medicare Prescription Drug

Improvement and Modernization Act of 2003 (Public Law 108-173, December 8, 2003)). The comment recommended that the essential-use designation for albuterol not be removed until generic albuterol HFA MDIs come on the market, to minimize spending by the Federal Government.

Although ~~C~~cost to the Federal Government is not a criterion under § 2.125(g) ~~and, therefore, cannot be considered in this rulemaking. In fact~~, the availability of prescription drug benefits under Medicare ~~will minimize~~ does affect whether patients are adequately served by the non-ODS products. In fact, the prescription drug benefits will reduce the impact of higher prices for albuterol MDIs on Medicare-eligible patients, who would not otherwise have prescription drug insurance benefits. This will help ensure that ~~all~~ patients are adequately served by albuterol HFA MDIs.

(Comment 22) A few comments suggested that prices for albuterol HFA MDIs would increase after the rulemaking. A GSK spokesperson at the PADAC meeting stated that GSK had committed to a price freeze on VENTOLIN HFA until December 31, 2007. The commitment was repeated in GSK's subsequent written comments.

We believe that GSK's price freeze will be effective in keeping prices at the current level through much of the transition period before the effective date of this rule. Although Schering has not made a similar commitment, it seems

unlikely that they will raise their prices knowing that one of their two competitors is committed to a price freeze. The presence of both GSK and Schering in the market should provide downward pressure on prices for albuterol HFA MDIs that will continue after the effective date of this rule (see pp. 13-20 of the National Economic Associates' comment of August 13, 2004 (2003P-0029/C25), and section V.D.1 of this document). Even if this pressure does not result in price decreases, it may prevent price increases. A representative of IVAX indicated at the PADAC meeting that IVAX's albuterol HFA MDI would be priced lower than PROVENTIL HFA and VENTOLIN HFA. IVAX's entry into the albuterol HFA MDI market and the potential market entry of additional albuterol HFA MDIs will provide additional ~~long-term~~ downward pressure on prices even before the entry of genric albuterol HFA MDIs.

(Comment 23) One comment objected to the elimination of the essential-use designation for albuterol MDIs, saying ~~that~~ the price of albuterol HFA MDIs is more than $100 per MDI compared to generic albuterol CFC MDIs, which cost less than $10 per MDI.

The issue of the impact of higher prices for albuterol HFA MDIs is one that we have given a great deal of thought, but the difference is not nearly as great as this comment states. The weighted average (across all payer types) of retail prescription price for generic albuterol CFC MDIs during the first half of

2004 was about $13.50 per MDI and the weighted average retail prescription price for albuterol HFA MDIs was about $39.50 per MDI (see section V.C.6. of this document). As we discuss in our response to comment 18 and section V of this document, we do not believe that this price difference prevents patients from using albuterol HFA MDIs.

(Comment 24) One comment recommended that we perform a cost-benefit analysis using Medical Expenditure Panel Survey (MEPS) data from the Agency for Healthcare Research and Quality (AHRQ).

The analysis of impacts described in section V of this document uses the MEPS data. While the analysis does look at both the costs and benefits of this rulemaking, we would not characterize the analysis as a full cost-benefit analysis because we are unable to fully quantify the public health costs and environmental benefits in dollar terms; however, we do quantify these costs and benefits to the extent we are able.

(Comment 25) One comment asserted that, while our analysis in the 2004 proposed rule of the economic impact of this rulemaking on patients was appropriate to the extent the analysis focused on whether higher prices would deter patients from using albuterol MDIs, those portions of the economic analysis that dealt with more general societal costs were inappropriate and contrary to the provisions of § 2.125.

We are required to examine the broader societal costs and benefits of any rulemaking. Executive Order 12866 directs us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The Regulatory Flexibility Act (5 U.S.C. 601-612) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires that agencies prepare a written statement that includes an assessment of anticipated costs and benefits before proposing any rule that includes any Federal mandate that may result in significant expenditure by State, local, and tribal governments, or the private sector.

(Comment 26) A few comments stated ~~that~~ albuterol HFA MDIs were unacceptable alternatives because they did not propel the drug with adequate force into the lungs. Other comments stated that they had to use an albuterol HFA MDI several times to get the same effect they had received from significantly fewer uses of an albuterol CFC MDI. Several comments from patients stated that their experience indicated albuterol HFA MDIs were less effective than albuterol CFC MDIs, while other comments from patients stated that they had found albuterol HFA MDIs to be more effective than albuterol CFC MDIs. One physician commented

that she believed HFA MDIs were better drug delivery systems than CFC MDIs.

The wording of certain comments leads us to believe that at least some of people submitting these comments may be confusing dry powder inhalers (DPIs) or aqueous (AQ) pumps with HFA MDIs. There are currently no albuterol DPIs or AQ pumps being marketed. We did not consider any DPI or AQ pump as a potential alternative to albuterol CFC MDIs. Other comments may reflect the common misperception that MDIs propel drugs into the lungs. MDIs do not in fact propel any significant amount of drug into the lungs. MDIs propel the drug into the mouth and the drug is then inhaled into the lungs. Albuterol CFC MDIs and albuterol HFA MDIs work in same way; both contain the active ingredient as a very fine powder which is delivered in a suspension into the patient's mouth. MDIs that forcefully deliver the drug suspension may actually be less effective at delivering the drug into the lungs. In these instances, a significant portion of the drug may be sprayed onto the surfaces in the back of the mouth, from which they will be swallowed rather than inhaled into the lungs. An explanation that we believe likely for some of these perceived differences is the possibility that the albuterol HFA MDIs that were being used~~ing~~ had clogged mouthpieces. Cleaning the mouthpieces as described in the

labeling for PROVENTIL HFA and VENTOLIN HFA should alleviate these problems.

Whatever the perceived differences between albuterol CFC MDIs and albuterol HFA MDIs may be, clinical studies have shown the albuterol HFA MDIs are as effective as the albuterol CFC MDIs in treating asthma and COPD.

(Comment 27) One comment stated ~~that~~ we should not remove the essential-use designation for albuterol MDIs because members of the person submitting the comment's family are allergic to the lactose contained in alternative products.

Neither VENTOLIN HFA nor PROVENTIL HFA contains lactose. While other inhaled drug products for the treatment of asthma and COPD do contain small amounts of lactose, our determination on the essential-use designation for albuterol MDIs is based exclusively on the suitability of VENTOLIN HFA and PROVENTIL HFA as alternatives.

(Comment 28) One person said in his comment ~~that~~ he had an adverse reaction that included tachycardia (elevated heart rate) after taking PROVENTIL HFA. He attributed the adverse event to ethanol, which is an inactive ingredient in PROVENTIL HFA and to which he is sensitive.

~~We are only aware of one report in our MedWatch system~~[10] Reports of an allergic reaction attributed to the very small amounts of ethanol contained in PROVENTIL HFA are extremely rare. VENTOLIN HFA, which does not contain ethanol, should be considered for asthma and COPD patients who may be sensitive to ethanol. Unlike the albuterol CFC MDIs, VENTOLIN HFA and PROVENTIL HFA ~~are~~ do not contain identical ~~products~~ active ingredients, and patients having difficulties with one product should discuss with their physicians switching to the other.

(Comment 29) One person said in his comment ~~that~~ he had an asthma attack after his first use of a QVAR (beclomethasone dipropionate) HFA MDI. He attributed the adverse event to the HFA propellant in the QVAR MDI and concluded that HFA MDIs would not serve patients who were sensitive to HFA.

Another person said in her comment ~~that~~ her use of an albuterol HFA MDI caused irritation and triggered an asthma attack.

A third comment suggested ~~that~~ HFA MDIs could be less likely to cause paradoxical bronchospasm because of tighter specifications for the various compounds in the MDIs.

Bronchospasm may occur after using any inhaled asthma drug, including both albuterol CFC and HFA MDIs. The approved

[10] MedWatch is the FDA safety information and adverse event reporting program, which allows health care professionals and consumers to report serious

labeling for both albuterol CFC and HFA MDIs, as well as QVAR and most other approved inhaled drugs, describe paradoxical bronchospasm as an adverse event that can be expected in a small number of patients. Paradoxical bronchospasm seems to be associated with the first use of an MDI or vial of an inhaled drug. The warnings about paradoxical bronchospasm represent a general concern with inhaled drugs, and do not represent a special concern for albuterol CFC and HFA MDIs or QVAR. Paradoxical bronchospasm is very rare; a study conducted in the United Kingdom of 10,472 patients regularly using VENTOLIN EVOHALER (an albuterol HFA MDI marketed in the United Kingdom that is substantially similar to VENTOLIN HFA) over five 3-month observation periods, did not show any incidents of paradoxical bronchospasm (Ref. 3). We have not seen any evidence from the clinical studies of various HFA MDIs that this type of adverse event is more or less common with HFA MDIs than with CFC MDIs. Absent other data, we cannot assume that the adverse events described in the comments were caused by the HFA propellant in the MDIs.

(Comment 30) A few comments stated ~~that~~ albuterol HFA MDIs left a powdery residue at the back of the throat. One person said in her comment that after using an albuterol HFA MDI she

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problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.

felt the need to rinse her mouth out. One comment said ~~that~~ this tendency to leave a powdery residue could lead to thrush and other infections.

A very small number of patients have reported an unpleasant powdery residue in the oral cavity after use of an albuterol HFA MDI. Any MDI can leave a residue in the oral cavity. Use of a spacer can minimize the amount of residue left in the mouth. Patients who experience this problem may wish to speak to their physicians about using a spacer with the MDI. We do not consider problems with a powdery residue to be either prevalent enough or serious enough to prevent patients from being adequately served by albuterol HFA MDIs.

Thrush, also known as candidiasis, is occasionally seen with the use of inhaled corticosteroids. Although thrush may be seen in patients who are taking both inhaled corticosteroids and inhaled albuterol, there is no evidence to suggest that use of albuterol or HFA contributes to the development of thrush. Accordingly, we do not believe thrush to be a problem with use of albuterol HFA MDIs.

(Comment 31) One comment stated ~~that~~ albuterol HFA MDIs are not an adequate substitute because they cannot be used with spacers.

Commercially available spacers can be used with both albuterol HFA MDIs. Patients who are having difficulties with

any MDI may wish to speak to their physicians about using a spacer in conjunction with the MDI.

We find that patients who medically require albuterol CFC MDIs are adequately served by albuterol HFA MDIs.

F. Effective Date

(Comment 32) Several speakers at the PADAC meeting and comments, including comments from Schering, 3M, and GSK, recommended an effective date of December 31, 2005.

Schering, 3M, and GSK have all stated that adequate production capacity and supplies would be in place by December 31, 2005. However, the December 31, 2005, date is merely a projected date, and neither Schering, 3M, nor GSK provided the basis for their projections. No timelines, construction and installation schedules, or training goals were provided to us. We have no descriptions of what new machinery must be procured, nor any idea when that machinery can be up and running. While we believe that the projections were made in good faith, unanticipated delays and shortages could push the date on which adequate production capacity and supplies are in place significantly beyond December 31, 2005. Due to the lack of underlying information, we are unable to evaluate the likelihood or length of any possible delays.

If this rule were to go into effect before adequate production capacity and supplies were in place, there would not

be a smooth transition from albuterol CFC MDIs to albuterol HFA MDIs. We could be forced to publish a notice postponing the effective date. We could see resumption of production at albuterol CFC MDI lines that had been closed and increased production to restock supplies of albuterol CFC MDIs that had been allowed to dwindle in anticipation of the effective date of this rule. If needed CFCs, MDI components, or production facilities were unavailable, shortages of albuterol MDIs could exist.

Futhermore, if we were forced to push the effective date of this rule back because of the failure of manufacturers to have adequate production capacity and supplies in place, it would be very harmful to any transition education program. Patients and health care providers would be provided with different dates by which the transition from albuterol CFC MDIs to albuterol HFA MDIs would be completed. This could lead to confusion, lack of trust, and the belief that people would not have to think about the transition because it would probably be postponed again.

When we consider how serious and life threatening asthma and COPD are, and how important albuterol MDIs are in treating asthma and COPD, it becomes apparent that a conservative estimate of when sufficient supplies and production capacity will exist and a later effective date will better ensure that shortages do not happen and a smoother transition will be made.

For these reasons we believe that a December 31, 2005, effective date does not provide an adequate safety margin to ensure that adequate production capacity and supplies will be in place. Accordingly, we have determined that December 31, 2008, is a more appropriate effective date for this rule.

We arrived at a December 31, 2008, effective date with the expectation that an orderly transition to albuterol HFA MDIs would be completed by that date. Although significant production and supplies may be in place prior to this date, in light of the serious consequences of inadequate supplies and the need to ensure that vulnerable patients have adequate access, the date of December 31, 2008 assures that the criteria in § 2.125(g) will be met and that the transition to albuterol HFA MDIs can be accomplished smoothly. This transition period between the publication of the final rule and the effective date ensures that new facilities will be on line, that manufacturers will have successfully demonstrated their ability to produce necessary supplies of albuterol HFA MDIs, and patients and health care providers will be adequately educated about the transition to albuterol HFA MDIs. In addition, after the effective date, section 610 of the Clean Air Act would prohibit the sales of albuterol CFC MDIs in interstate commerce. As discussed below in response to comment 42, the transition time

under this rule will allow for retailers and their suppliers to deplete their stock.

~~We arrived at a December 31, 2008, effective date with the expectation that the transition to albuterol HFA MDIs would be well on its way to completion by the end of 2007 based on information provided by manufacturers of albuterol HFA MDIs. We believe that the albuterol CFC MDI production in 2008 will be characterized by producers drawing down on preexisting stocks of bulk CFCs as well as selling previously manufactured albuterol CFC MDIs. Although, we feel~~ believe ~~that adequate production and supplies should be in place by December 31, 2007, we believe that a one-year safety margin is prudent, in light of the serious consequences of inadequate supplies, we believe that a one-year safety margin is prudent. This safety margin better ensures that new facilities will be on line, that manufacturers will have successfully demonstrated their ability to produce necessary supplies of albuterol HFA MDIs, and that the transition to albuterol HFA MDIs can be accomplished smoothly.~~

(Comment 33) One comment suggested a 2007 effective date without giving reasons why this date would be more appropriate than others.

This comment did not provide any information or rationale for the date, and our rationale for the December 31, 2008, effective date is set out in our response to comment 32.

(Comment 34) A few comments asked that we set an effective date that will allow patients to try different albuterol HFA MDIs to see if they perform adequately for individual patients.

We would like to point out that PROVENTIL HFA was introduced into the U.S. market in 1996 and VENTOLIN HFA was introduced into the U.S. market in February 2002. Patients have had a significant period of time to try these drug products and we do not feel additional time is necessary or, based on the number of albuterol HFA MDIs currently being sold, that large numbers of patients will voluntarily avail themselves of the opportunity to try albuterol HFA MDIs. In any event, we believe the December 31, 2008 effective date provides ample opportunity for patients to work with their healthcare providers to determine the best substitute.

(Comment 35) Several comments urged us to set the effective date for this rule late enough to allow lower-priced generic albuterol HFA MDIs onto the market before the essential-use status of albuterol MDIs is removed.

As we discussed in our responses to comment 18 and in section V, we do not believe that presence of generic albuterol HFA MDIs is necessary to ensure that patients are adequately served by albuterol HFA MDIs.

(Comment 36) In the 2004 proposed rule we asked for comments "on when patents may cease to bar the marketing of

generic albuterol HFA MDIs." (2004 proposed rule at 33608.) We did not receive any substantive comments on this issue. One comment, while agreeing with us that we do not have the institutional expertise to evaluate patents, criticized our statement that "it seems at least possible that key patents could be successfully challenged well before 2015 or perhaps even 2010, allowing generic drugs to enter the market much earlier than anticipated." (2004 proposed rule at 33608.) The comment asserted ~~that~~ it would be irresponsible to base any decision on the mere possibility that patents may be successfully challenged. The comment also stated ~~that~~ competition would not be blocked because of the ability of firms to license HFA MDI technology from 3M. It also pointed to IVAX as a potential source of competition.

~~Because w~~We did not receive any substantive comments on the validity of the patents listed in the Orange Book for albuterol HFA MDIs.~~, we are publishing this rule based on the assumption that no generic albuterol HFA MDIs will enter the market before the expiration of the last listed patent in 2017.~~[11] Because we have determined that, as we discussed in our response to comment 18 and in section V, the presence of generic albuterol HFA MDIs in the market is not necessary to ensure that patients are

[11] ~~Since publication of the 2004 proposed rule, two patents that expire in 2017 have been listed in the Orange Book for VENTOLIN HFA.~~

adequately served by albuterol HFA MDIs it is not necessary for us to reach a conclusion on the validity of those patents. We do not believe that IVAX or entrants into the albuterol HFA MDI market that license HFA MDI technology from 3M will be priced as low as current generic albuterol CFC MDIs. We base this belief on the added expense that licenses will entail for manufacturers and the past history of drug pricing. However, we do believe that IVAX and other, potential, ~~these~~ entrants can exert downward pressure on prices that could result in lower prices than we currently see for albuterol HFA MDIs. ~~In any event, we have determined that, as we discussed in our response to comment 18 and in section V, the presence of generic albuterol HFA MDIs in the market is not necessary to ensure that all patients are adequately served by albuterol HFA MDIs.~~

(Comment 37) A representative of Honeywell, speaking at the PADAC meeting, said ~~that~~ Honeywell planned to resume production of CFC propellants at a Louisiana plant, and gave assurances that Honeywell Chemicals could supply CFC propellants for years to come, if needed. He also said ~~that~~ FDA should not consider a shortage of CFC propellants in establishing a transition strategy. Honeywell later provided more details on the subject in a written comment.

Another speaker at the PADAC meeting said ~~that~~ Honeywell's resumption of production at their Baton Rouge plant would

violate U.S. law and the Montreal Protocol. He further said that according to statements made by Honeywell, current stockpiles of CFCs coupled with production of CFCs at Honeywell's Netherlands facility, which is scheduled to close at the end of 2005, should meet U.S. demand for CFCs for use in MDIs until 2008.

~~We received a late comment disputing assertions that Honeywell made about the Baton Rouge facility's compliance with the Montreal Protocol and the Clean Air Act.~~

Another comment stated ~~that~~ it was appropriate for us to take into account the disruptions in the supply of CFCs caused by Honeywell ending production of CFCs at their Netherlands facility and the equivocal legal status of Honeywell's resumption of production of CFCs at their Baton Rouge facility. It also said ~~that~~ we should carefully scrutinize Honeywell's ability to manufacture pharmaceutical grade CFCs at the Baton Rouge facility.

Although~~,~~ we discussed Honeywell's continued production of CFCs in the 2004 proposed rule (2004 Proposed Rule at pp. 33607-33608), this issue does not address any of the criteria under which we are making a determination on the essential-use status of albuterol MDIs. The criteria in §2.125(g) direct us to examine the adequacy of supplies and capacity for the non-ODS

substitutes, but not the supplies and capacity for the ODS product.

(Comment 38) Speakers at the PADAC meeting and written comments stated that the Parties to the Montreal Protocol were unlikely to continue to approve the United States' future nominations for allocations of CFCs for use in MDIs. One comment asked that we carefully consider the future supply of CFCs in setting an effective date for this rule. Another comment pointed out that a key raw material in the production of CFCs is carbon tetrachloride, an ODS that is being phased out under the provisions of the Montreal Protocol. The comment asserted that this could lead to a situation where it could be very difficult to obtain the needed raw materials for the manufacture of CFCs, even if the manufacture itself was allowed under the Montreal Protocol. Another comment urged us to not allow the fact that other Parties to the Montreal Protocol have initiated phaseouts of albuterol CFC MDIs pressure us into a premature action, pointing out that prices for albuterol HFA MDIs are lower in other countries.

We are obligated to follow the procedures and criteria in § 2.125 in this rulemaking, and the continued supply of CFCs under the Montreal Protocol or the phaseout strategies in other countries are not criteria listed in